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Tramadol HCL: Preformulation Studies of Imperative Part of Formulation Design

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Abstract | **Original Research Article**

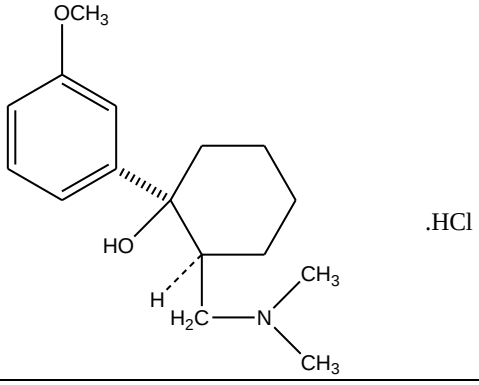
Preformulation study is a part which is initiated formerly the new molecule is seeded. In a broader way, it pact with studies of physical, chemical, analytical, and pharmaceutical properties related to molecule and provides idea about suitable modification in molecule to show a better performance. Preformulation parameters study can be linked to production of effective, safer, stable, and reliable pharmaceutical formulation. Tramadol is an opioid pain medication used to treat moderate to moderately severe pain. The mechanism of action is not clear, even though the parent and metabolite of Tramadol binds to μ-opioid receptors and results in weak inhibition and reuptake of nor-epinephrine and serotonin. In the present works generally goal of preformulation studies of Tramadol HCl is to engender information useful in developing stable and Bioavailable dosage forms.

Keywords: Preformulation study, Tramadol HCl, Solubility & analytical methods.

INTRODUCTION

Preformulation study is the chief tread in the rational development of dosage forms of a drug substance. The study includes an examination of physical and chemical properties of a drug substance alone and with combined with excepient. The general endeavor of preformulation testing is to generate information helpful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. Preformulation investigations are designed to deliver all necessary data especially physicochemical, physico-mechanical and bio pharmaceutical properties of drug substances, excipients and packaging materials [1]. These studies should focus on those physicochemical properties of the new compound that could affect drug performance and development of an effective dosage form. A systematic understanding of these properties may eventually provide a rational for formulation design, or sustain the need for molecular modification. The aim of this study was to establish some of the physicochemical properties such as solubility, melting point, pKa, dissolution, assay development, stability in solution etc [2, 3].

Tramadol hydrochloride, (±) cis-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol Hydrochloride [4]. Tramadol Hydrochloride is a narcotic like analgesic used in severe pain. Tramadol has inhibitory action on 5-HT2C receptor and even though the parent and M1 metabolite of Tramadol binds to μ opioid receptors and results in weak inhibition and reuptake of norepinephrine and serotonin. In several animal tests Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone [5].

Drug (Tramadol hydrochloride) description [6, 7]	
IUPAC Name	(±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol Hydrochloride
Structure	 .HCl
Molecular formula	$C_{16}H_{25}NO_2$. HCl
Molecular Weight	299.8
Nature	White, bitter, crystalline and odorless powder
Solubility	It is readily soluble in water and ethanol
Therapeutic category	Opioid analgesic

In the present works a challenge was made to study preformulation parameters of Tramadol HCl which helps to produce information useful in developing stable and Bioavailable dosage forms.

MATERIAL AND METHODOLOGY

Procurement of Drug: Tramadol hydrochloride was obtained as gift sample from JubilantChemsys Ltd., Noida.

Organoleptic properties

Organoleptic properties of the drug sample were studied by visual inspection.

Preformulation studies [8-16]

Identification of Drug

Melting Point Determination

To determine the M.P. of drug powder, it was filled in a capillary tube with one end open and the other end closed and then the capillary was placed in a digital melting point apparatus.

Solubility

The drug was found to be freely soluble in water and in methanol, very slightly soluble in acetone, which matches the existing reference.

Loss on drying

The average LOD (%w/w) and % LOD were determined.

Partition coefficient

About 50mg of drug was dissolved in 50ml of distilled water and n-octanol separately and both the solution was mixed together by using wrist watch shaker for 30 min. Then the solution was kept in a separating funnel until two phases separated. The aqueous phase was then filtered through the filter paper and was diluted 100 times. The absorbance of both the solutions was taken at 234nm by using UV spectrophotometer. The concentration of drug was determined with the help of standard curve and partition coefficient was determined by following formula:

$$\text{Partition coefficient} = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous}}$$

FTIR spectroscopy studies

FTIR (ATR Bruker, Germany) was used. The IR spectrum was obtained by scanning it in the range 4000-500nm and compared with the reference pharmacopoeia (IP-2014).

Analytical Method

A concentration 1.0 µg/ml solution of tramadol hydrochloride in distilled water was scanned. The scan report is shown in fig. no.1 and the λmax was found to be 270 nm.

Preparation of standard curve in distilled water

As described in experimental section, the different dilutions were analyzed in UV-Spectrophotometer at 270 nm and the standard curve was plotted. The graph obeyed the Beer- Lambert's law, the regression equation of the curve is found to be y = 0.1613x + 0.0485 and correlation coefficient is found to be 0.9999, which reveal high precision of curve. This curve is further used for drug content analysis.

UV-analysis of tramadol hydrochloride in phosphate buffer pH 7.4

A solution of tramadol hydrochloride in phosphate buffer pH 7.4 of conc. 0.8 µ/ml was scanned. The λmax was found to be 271 nm.

Preparation of standard curve in phosphate buffer pH 7.4

The λmax is found to be 271 nm. The graph obeyed Beer-Lambert's law at the range of 2-20 µg/ml, the regression equation of the curve is found to be y = 0.1688x + 0.0057 and correlation coefficient is found to be 0.9992 made the method suitable and precise for further analysis of drug during in- vitro release study.

Table 1: Preformulation Characteristics

S. No.	Characteristics	Results
1.	Appearance	White, bitter, crystalline
2.	Melting Point	Melting Point was found to be 180℃-184℃.
3.	Partition coefficient	1.32

Table 2: Solubility data of the drug in different solvents/ buffers

Solvents	Conc. mg/ml at room temperature	Solubility
Water	30 mg/ml	Freely
Methanol	22 mg/ml	Soluble
Acetone	10.2 mg/ml	Freely
Phosphate Buffer pH 7.4	>20 mg/ml	Soluble Slightly Soluble Sparingly Soluble

Table 3: Percent loss on drying of tramadol hydrochloride

S. No.	wt. of before drying(gm)	wt. of after drying(gm)	LOD(%w/w)	Average LOD(%w/w)	Limit of LOD(%w/w)
1	1	0.9985	0.15	0.15	0.1-0.5
2	1	0.9986	0.14		
3	1	0.9985	0.15		

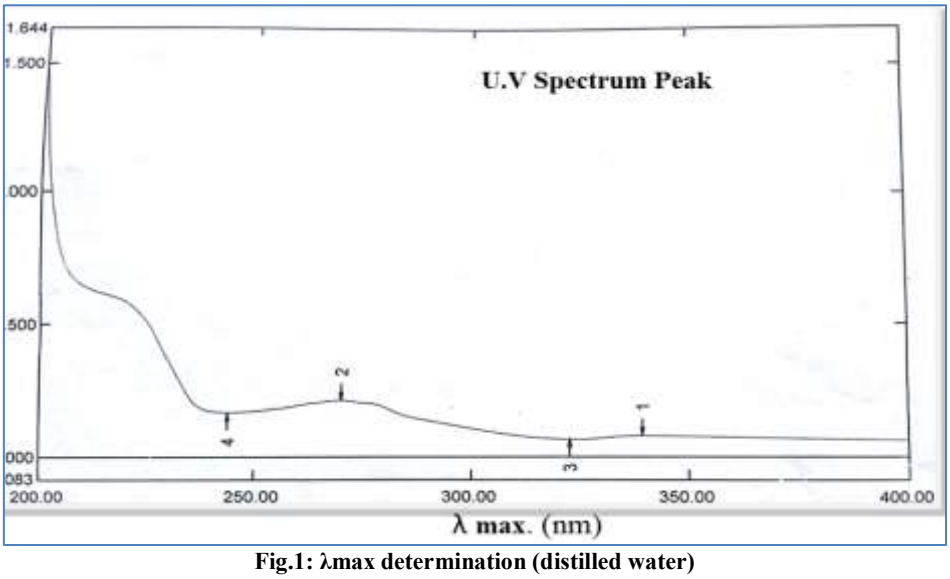


Fig.1: λmax determination (distilled water)

Table 4: Standard curve data of tramadol hydrochloride in distilled water

S. No.	Conc.(µ/ml)	Absorbance
1	0.2	0.081
2	0.4	0.112
3	0.6	0.145
4	0.8	0.180
5	1.0	0.209
6	1.2	0.241
7	1.4	0.275
8	1.6	0.308
9	1.8	0.338
10	2.0	0.371

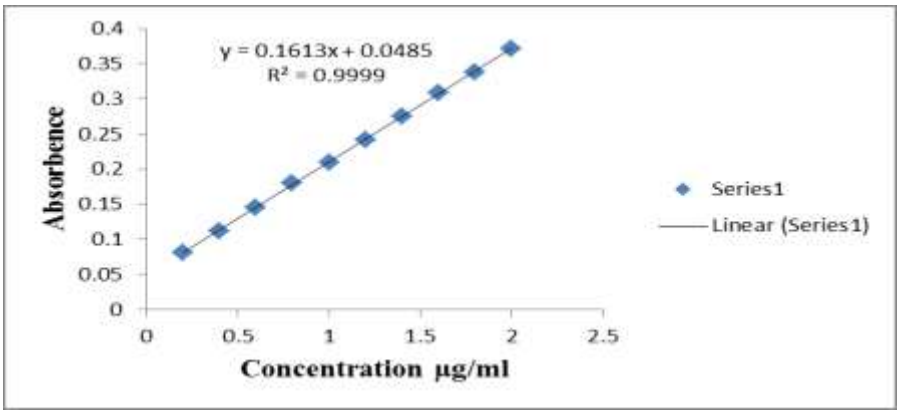


Fig-2: Standard cuve of Tramadol

Table-5: Standard curve data of tramadol hydrochloride in in phosphate buffer pH 7.4

S. No.	Conc.(µ/ml)	Absorbance
1	0.2	0.039
2	0.4	0.072
3	0.6	0.105
4	0.8	0.140
5	1.0	0.181
6	1.2	0.210
7	1.4	0.242
8	1.6	0.272
9	1.8	0.307
10	2.0	0.345

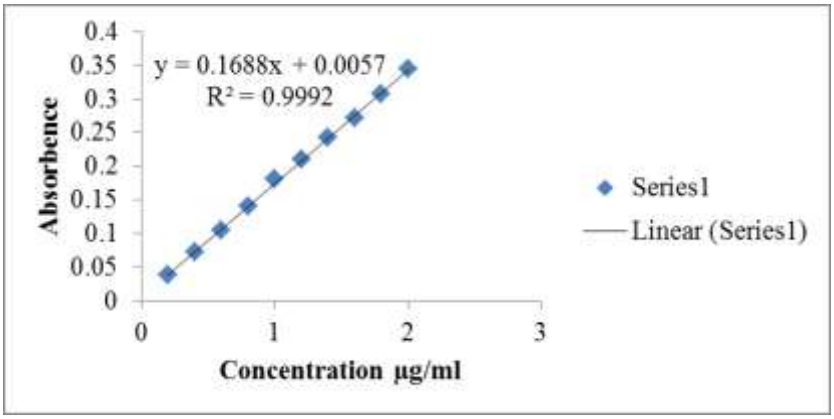


Fig-3: Standard curve of TH in phosphate buffer pH 7.4

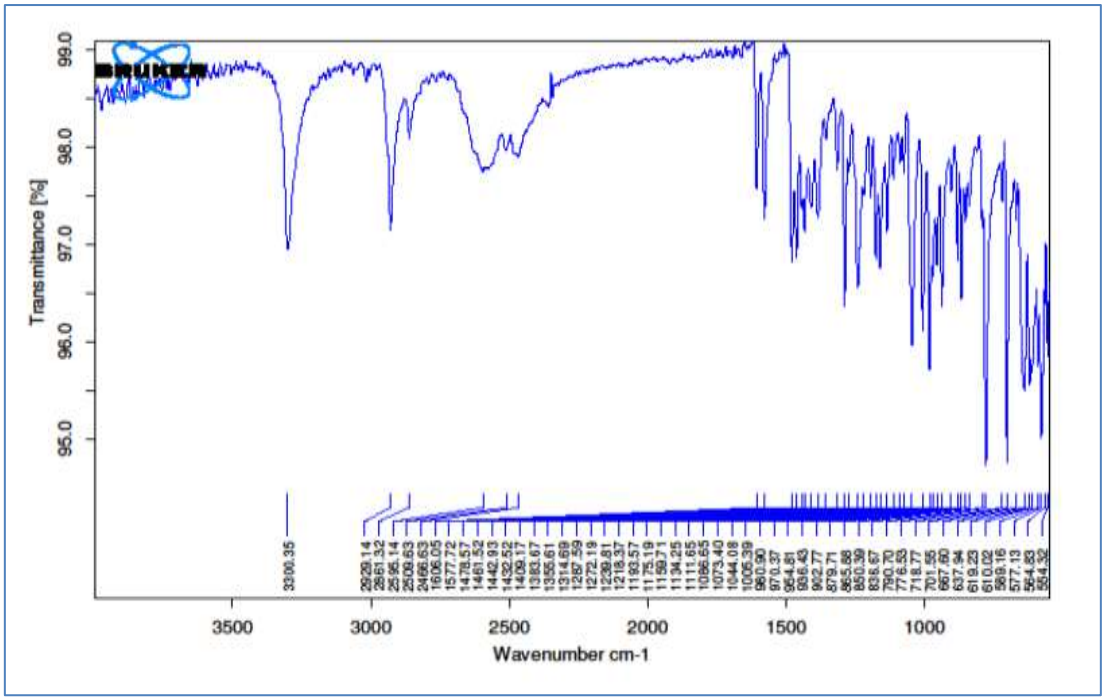


Fig-4: IR spectra of standard Tramadol

Table-6: Interpretation of IR spectrums

Sample	Obtained peak values(cm^{-1})	Theoretical frequency(cm^{1})	Functional group
Tramadol HCl	3100	3500-3100	Secondary Amines (-NH) Str
	1462	1450-1600	C=C(S)
	2961	2960-2850	Methyl (-CH) Str.
	938	900-1300	C-O(S)
	1040	1000-1410	Amine C-N(S)
	852	800-1200	C-C(S)

RESULTS AND DISCUSSION

The in general purpose of the present work was to investigate preformulation studies of Tramadol HCl is to generate information useful in developing stable and Bioavailable dosage forms. Preformulation studies of drug were undertaken concerning melting point, solubility analysis, UV-spectrophotometric analysis and FTIR analysis to identify and assessment of purity of drug. Various Preformulation Characteristics were tabulated in table 1. The partition coefficient of rutin was found 1.32, which confirms the lipophilicity of the drug. The drug was found to be freely soluble in water and in methanol, very slightly soluble in acetone, which matches the existing reference. From the result reported in the table 3 revealed that the loss of drying of the drug is within range 0.1-0.5. The analytical method for determination of drug was UV spectroscopy. The absorption spectral analysis showed the λ_{max} of Tramadol HCl at 270 & 271 nm in distilled water and phosphate buffer pH 7.4 respectively (table 4-5 & Fig.1-3). The calibration data and curve is shown in table no. 4 and figure no. 2 respectively. The result of UV- Spectrophotometrically analysis in phosphate buffer is shown in table no. 5 and figure no. 3. The FTIR spectrum, there was no variation in the Tramadol HCl peaks from the standard spectrum of IP 2014(fig 4).The result of interpretation of IR spectra was tabulated in table 6 . Preformulation studies revealed the purity of the drug. UV-spectrophotometric analysis of drug in distilled water and phosphate buffer pH 7.4 ($y = 0.1613x + 0.0485$, $R^2 = 0.9999$ in distilled water and $y = 0.1688x + 0.0057$, $R^2 = 0.9992$ in phosphate buffer pH 7.4) revealed the suitability of the standard curve for further calculation.

CONCLUSION

The preformulation step is a fundamental fraction in establishing the properties of drug that will allow suitable risk assessment for development. Usually it begins all through the lead optimization phase, continues through predomination, and on into the early on phases of development. Hence, it is necessary that preformulation should be performed as carefully as possible to facilitate coherent decisions to be made. The preformulation study of Tramadol HCl is to make information useful in developing stable and Bioavailable dosage forms.

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